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Process for the preparation of tetrazole derivatives in a new crystal form

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REPUBLIC OF SLOVENIA
MINISTRY OF SCIENCE AND TECHNOLOGY

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REQUEST FOR A PATENT GRANT

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Acknowledgement of the application
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2. Applicant (Family name followed by given name and address; for a legal entity, full official designation

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5. Title of invention:

Process for the preparation of tetrazole derivatives in a new crystal form

6. Claimed priority right:

7. Additional requests:

☐ application for a shortened duration patent
☐ preliminary publication after the expiry of ___months
☐ application is divided from the application no.:___

8. Statements:

☐ statement of common representative

9. Enclosures:

x Description of the invention, having 17 pages
x Patent claim (claims), having 2 pages; number of claims: 18
x Schemes (if required for patent description); number of sheets: 8
x Abstract
☐ Voucher for the settlement of fees
☐ Declaration of depositing the biological material if it is an invention which cannot be described
☐ Authorisation to the representative
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☐ Declaration on priority right
☐ Information about additional applicants
x Information about additional inventors
☐ Presentation of nucleotide or amino acid sequence in the description
☐ Application was previously faxed or mailed in electronic form
☐ _____

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11 June 2003 Our Ref: pš-543 Your Ref:

Annex to the request for a patent grant

Information about additional inventors:
Preparation of tetrazole derivatives in a novel crystal form

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Process for the preparation of tetrazole derivatives in a new crystal form

Field of the invention

(IPC[7] C 07 D 403/10, A 61 K 9/19)

The present invention belongs to the field of chemistry of heterocyclic compounds and pharmaceutical industry and relates to a novel crystal form of a pharmaceutically useful crystalline potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole with the bound water and the new mode of its preparation.

Technical problem

2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole, known under the generic name losartan, acts on the last step of the cascade renin-angiotensin system by binding to the angiotensin II receptor. By utilizing said biochemical effect losartan is generally used as an effective antihypertensive agent in the form of a potassium salt (hereinafter referred to as losartan potassium). In pharmaceutical compositions it is often combined with diuretics.

There is a need for losartan and the salt thereof, respectively, of high purity in such a form to be simply incorporated into a pharmaceutical formulation which provides high bioavailability. For incorporation into a pharmaceutical formulation, pharmaceutical active substances must have defined desired physicochemical properties and in addition to high purity, suitable stability, nonhygroscopicity, appropriate solubility and compatibility with the excipients are demanded.

Prior art

The substituted imidazoles with an action on the renin-angioten system of the blood pressure regulation are disclosed in the patent EP 253310 and US Pat. No. 5,138,069. In the experimental part, it is shown that in the synthesis of losartan from a cyanobiphenyl intermediate (that is, from 2-*n*-butyl-4-chloro-1-[(2'-cyanobiphenyl-4-yl)-methyl]-5-(hydroxymethyl) imidazole) with sodium azide losartan is produced in a form of slightly yellow crystals.

It is known that losartan potassium exists in two polymorphic forms [K. Raghavan et al., Pharm. Res., 1993, 103 900-904; L. S. Wu et al., Pharm. Res., 1993, 10, 1793-1795]. The authors of US Pat. No. 5,608,075 present that polymorphic form I, characterized by DSC endotherm at 229.5°C, while heating transforms to polymorphic Form II characterized with the endothermic peak of melting at 273.2°C. Form I is stable at room temperature, Form II is stable at higher temperatures. Therefore, Form II gradually converts to thermodynamically more stable Form I under normal conditions of handling.

Further, crystal and crystalline forms of acid addition salts of losartan are known from US Pat. No. 6,350,880 and EP 1106611.

EP 324377 describes the process for the formation of a potassium salt of losartan with an aqueous potassium hydroxide solution, and a similar process for the formation of crystalline losartan potassium in polymorphic form I is disclosed in WO 02094816 where, unlike the said process, instead of an aqueous solution of potassium hydroxide, solid potassium hydroxide is added to an alcoholic solution of losartan.

According to the process of the synthesis disclosed in US Pat. No. 5,130,439 and US Pat. No. 5,310,928, crystalline losartan potassium of form I is formed *via* substituted boric salts with hydrolysis of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole with sulfuric acid in tetrahydrofuran and subsequent rinsing on the column with dipotassium hydrogen

phosphate and by concentrating the rinsed aqueous solution with added *i*-propanol.

A defined form of the polymorph itself does not provide demanded suitable physicochemical properties. In US Pat. No. 5,859,258, losartan of polymorphic form I was crystallized from a mixture of *i*-propanol and 2.4–2.6% of water. It has been found that uncontrolled crystallization may result in formation of large three-dimensional complexes which are inappropriate for incorporation into a pharmaceutical formulation, and the patent discloses the very rigorously controlled process demanding fulfilment of 14 different conditions in order to obtain the desired morphology of the particles for pharmaceutical use.

For the compound 2-*n*-butyl-4-spirocyclopentan-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphnyl]-4-yl]methyl]-1H-imidazolin-5-one, structurally related to 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole, in US Pat. No. 5,292,331 it has been found it crystallizes in one polymorphic form from nonaqueous solvents, and the other polymorphic form from solvents with more than 10% water, calculation of the basic cell made from a monocrystal of the other form suggests that despite a large amount of water in a crystallization solvent a polymorphic form is not in the form of a hydrate and it does not include crystal-bound water, respectively.

Description of the figures

Figure 1: A photograph of the crystal of polymorphic form III of a potassium salt of losartan made in the radiation polarization light

Figure 2: A thermogram of polymorphic form III of a potassium salt of losartan

Figure 3: DVS diagram of polymorphic form III of a potassium salt of losartan

Figure 4: DSC curve of polymorphic form III of a potassium salt of losartan

Figure 5: DSC curve of an amorphous potassium salt of losartan

Figure 6: X-ray powder diffractogram of polymorphic form III of a potassium salt of losartan

Figure 7: X-ray powder diffractogram of an amorphous potassium salt of losartan

Figure 8: X-ray powder diffractograms of a potassium salt of losartan made by recording the sample of polymorphic form III of potassium salt of losartan at different temperatures.

Description of the invention

The present invention provides a completely new crystal form of losartan potassium with the bound water and the process for the preparation of new crystalline form wherein the presence of water is an essential element.

In our research work we have found that lyophilization of an aqueous solution of the alkali or alkali-earth salt of losartan or evaporation affords the active substance in the form of a fine amorphous powder.

From the amorphous structure in a humid atmosphere a new crystal form is produced containing the bound water because we have found that an amorphous substance is hygroscopic and binds water whereupon the system is re-ordered into a crystal structure which, for example, occurs at room temperature at about 80% relative humidity.

In the further study of the new crystal structure it has been surprisingly found that losartan potassium in said form is less water soluble than losartan potassium of known anhydrous form I or an amorphous form and is, therefore, formed in a solid state from the solution prepared from losartan potassium and a small amount of water in 0.4 to 1.2-fold the weight of losartan. From the resulting formed mass losartan potassium in a novel form is produced by drying and grinding.

It is technologically more convenient if a solid substance is isolated by filtration or centrifuging than by crushing of the solidified mass, therefore, a water immiscible solvent is added to a dense aqueous suspension whereupon the residue is dissolved in the suspension which is then easily filtered or centrifuged.

Under the specific conditions, losartan potassium is re-ordered into a crystal structure with the bound water also during mixing in a mixture of nonpolar hydrophobic solvents and water or if a smaller amount of water is added to losartan suspension in such solvent or if a solvent immiscible or poorly miscible with water is added to the saturated aqueous solution of losartan.

In there is proportionately much water in a mixture of solvents losartan dissolves in it, if there is too little water conversion is incomplete or too slow. We have surprisingly found that a crystal structure with the bound water may be optionally isolated if a molar ratio of water corresponds to only about 20% of overage of 3-fold molar ratio (weight ratio 0.14) of losartan.

Solvents, combined with an appropriate molar amount of water from which isolation of the new crystal form of losartan potassium containing the bound water is feasible, for example, include water immiscible ethers (diethyl, diisopropylether, t-butylmethylether), hydrocarbons (pentane, hexane, heptane), cyclic hydrocarbons (cyclohexane, methylcyclohexane), aromatic hydrocarbons (benzene, toluene, xylene), esters (ethyl acetate, isopropyl acetate, n-butyl acetate) and combinations thereof.

The new crystal form may be also obtained from known Form II but, the conversion may be slower or incomplete due to smaller solubility in water.

Conversion in solvents comprising from 0.11- to 1.2-fold weight overage of water to losartan weight appears to be successful.

The most suitable process for the preparation of the new crystal form of losartan potassium with the bound water is as follows: a potassium salt of losartan is suspended in diethylether. While stirring vigorously, water is added to the suspension at room temperature. Molar overage of water to losartan is from about 3 to about 30, preferably from about 3 to about 12. The suspension is stirred overnight and the precipitate formed is filtered off and dried.

If solvents or mixtures of solvents in which water is poorly soluble are used a molar overage of water to losartan should be closer to 3.

A crystal form of a potassium salt of losartan with the bound water characterized with the peak diffractions in X-ray powder diffractogram at about 13.0, 17.2, 19.7, 20.9, 21.0, 23.2, 23.6, 24.5, 25.0, 26.6, 17.3, 28.2, 29.0, 31.5 degrees 2θ was named polymorphic form III.

Characteristic for polymorphic form III is that it contains bound between about 7% and about 13% of water. In the thermogravimetric analysis of the sample of form III the following takes place: water is lost in two steps. In the first step, the sample loses 4% of the weight to about 55°C, in the second, to about 8%, totally about 12%.

The present invention also relates to pharmaceutical compositions containing an alkali or alkali-earth salt of losartan in the crystal form with the bound water. Preferably, pharmaceutical compositions containing polymorphic form III of losartan potassium are the object of the present invention. The appropriate daily dose contains 1 to 500 mg of polymorphic form III of losartan potassium and may also comprise the other suitable active substances, for example, a diuretic.

The pharmaceutical composition may be in a dosage form suitable for oral or parenteral administration and is indicated, for example, for the treatment of hypertension, the pharmaceutical composition, the object of said invention, can be in the form of tablets, capsules, pellets, granules and suppositories. Solid pharmaceutical dosage forms can be coated, for example with the aim to improve pelletability, or to adjust disintegration and absorption, respectively.

According to the object of the present invention, we have prepared film coated tablets by the method of the direct dry blend. Thus, in one of the examples, tablets were prepared from the following ingredients: losartan potassium, anhydrous lactose, perlitol, ac-do-sol and PVK K 252, magnesium stearate, aerosol and

compritol. Optionally, a film coating prepared as a suspension from hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide was applied onto the cores, and resulting film-coated tablets were polished with talc. Pharmaceutical compositions containing polymorphic form III can be also prepared by the other convenient methods, for example, by the dry granulation method.

Experimental part

Crystalline forms of losartan prepared by conversion of the amorphous substance in humid atmosphere or prepared from the amorphous substance in one of known polymorphic forms by crystallization from a mixture of water and a solvent immiscible or poorly miscible in water were mutually compared and in all examples it was found to be novel polymorphic form III, and it was described and characterized by the following physicochemical methods:

1. Thermogravimetric analysis (TG)
2. Dynamic vapour sorption (DVS)
3. Differential thermal calorimetry (DSC
4. X-ray powder diffraction (XRD)
5. Dependence of XRD upon temperature.

1. Thermogravimetry (TG):

The measurement was carried out on a thermo analyzer Mettler Toledo TGA/SDTA 851e in 150 ml platinum crucibles diameter 7 mm in a dynamic atmosphere of air with a flow rate of 100 ml/min. Heating rate 5°C per minute from 25°C to 240°C. The base curve was subtracted from the measurement and was stopped at 240°C.

Figure 2 represents the loss on weight at heating the sample of 10.17 mg of polymorphic form III of losartan potassium.

2. Dynamic Vapour Sorption (DVS):

The test was performed on an instrument DVS – The Sorption Solution, Surface Measurement Systems Ltd, UK.

The above method refers to the following principle: the test sample is placed on one side of the very precise balance, and the reference nonhygroscopic sample on the opposite side. The balance with the samples is in the isolated chamber with feasible control or adjustment of the surrounding relative humidity. A hygroscopic sample binds humidity from the surrounding atmosphere resulting in weight change, said change is visualized on the balance.

Relative humidity, that is, relative moisture denotes a percentage of moisture in the atmosphere, or a quotient of the water partial pressure in the atmosphere to water vapour pressure at the specified temperature. Water vapour pressure is the maximum partial pressure which may be achieved by water at the specified temperature – at that pressure the relative humidity is 100%. Water vapour pressure depends on the temperature: it is 3.07 kPa at 25°C, 101.32 kPa at 100°C. The higher the relative humidity of the ambient atmosphere is, the more water may be absorbed by the hygroscopic substance. Here, the equilibrium is reached between the bound water in the substance and the vapour water in the atmosphere. If the relative humidity of the atmosphere is increased, the hygroscopic substance additionally absorbs the water and the new equilibrium is reached again. These equilibriums are visualized on the DVS instrument as the dependence of the sample weight upon the relative humidity in the atmosphere. In the sample water may be bound in the form of free moisture or is bound on the precisely defined sites in the crystal lattice and is named crystal-bound water. Crystal water is usually in the molecule in the stoichiometric relationship. It is bound more strongly than free absorbed moisture and usually exists simultaneously in the stoiochiometric number.

Humidifying:

According to the similar principle, as described to reach the equilibrium between the sample moisture and the atmospheric moisture, different equilibrium relative moisture in an air-tight space (desiccator) may be reached with different salts and

their concentrations in the solution. In our experiment of humidifying amorphous losartan potassium, an atmosphere of the air with 80% relative humidity was used, thus, at 25°C the pressure of that water was 2.46 kPa.

DVS experiment is presented in Figure 3. The ordinate denotes a change of the weight, the abscissa change pf humidity. Curve (◇) denotes an increase of the weight of amorphous losartan potassium denoting water absorption to 25% at 80% RH, then polymorphic form III is crystallized which is visualized as a drop of the weight above said relative humidity of the ambient (water content in the sample is about 13%); (□) denotes a change of the weight of resulting polymorphic form III with reducing relative humidity, and at relative humidity below 20% the sample loses crystal water and becomes amorphous again; (△) denotes anew water sorption to about 13% at 60% RH, then the amorphous sample crystallizes to polymorphic form III; (○) denotes a change of the weight of polymorphic form III with reducing relative humidity, at relative humidity below 20% the sample loses crystal water again and becomes amorphous again.
From the results, it is evident that crystallization from the amorphous substance to the polymorphic form III with the moisture increase is repetitive as well as the formation of the amorphous substance from polymorphic form III with reducing environmental relative humidity is repetitive.

3. Differential thermal calorimetric analysis (DSC)

A differential dynamic calorimeter Perkin Elmer Pyris 1 DSC was used.
The measurement was performed by the following protocol: sample weight: 1.2 mg, heating: 1 min at 30°C, then heating 30 to 320°C with the rate of 10 K/min

A DSC thermogram of the polymorphic form III of a potassium salt pf losartan.

To 75°C a stretched peak is visible denoting loss of first water, about 90°C a sharp endothermic peak which is probably simultaneous loss of the other two waters and destruction of an ordered state to amorphous (an amorphous form of the substance has a higher level of disordered state and thus higher entropy than

a crystalline form, therefore, conversion of a crystal to an amorphous form is an endothermic process). At 190–200°C the amorphous substance crystallizes again.

A DSC thermogram of the amorphous potassium salt of losartan.

To 110°C a stretched endothermic peak is visible denoting loss of water. At 128–129°C there is a saddle denoting a glassy conversion of the amorphous substance. At 201–220°C there is a well-marked peak resulting from the ordered state of the structure into the crystal lattice. Crystals of the substance begin to melt at 273°C, melting is followed by decomposition, being the same as in the crystalline substance.

DSC thermograms are shown in Figures 4 and 5.

4. X-ray powder diffraction analysis (XRD)

The samples were recorded on an apparatus Philips PW1710 using the reflexion technique under the conditions: CuKα radiation, range from 2° to 37° 2θ with a 0.04y 2θ step, integration time 1 second.

X-ray powder diffractograms of the samples of polymorphic form II of losartan potassium, irrespective of the mode of their preparation, indicate distinct bands at the angles at about 13.0, 17.2, 19.7, 20.9, 21.0, 23.2, 23.6, 24.5, 25.0, 26.6, 17.3, 28.2, 29.0, 31.5 degrees 2θ, which are distinctive from those from the prior art characteristic for polymorphic form I. A typical diffractogram is shown in Figure 6. For comparison, a typical diffractogram of amorphous losartan potassium salt is shown in Figure 7.

5. Dependence of XRD upon temperature:

The sample of polymorphic form III of losartan potassium was measured on an apparatus Siemens D5000 using the reflexion techniques at the low temperature

setting under the conditions: CuK radiation, range from 2° to 37° 2θ with a 0.04° 2θ step, integration time 4 seconds, divergence slit V6, entrance slit 0.6 mm.
The sample was measured at different temperatures. Heating to individual temperature was at the rate of 10°C/min. Measurement at one temperature lasted 59 minutes. Total time of the measurement was 7 hours and 22 minutes. That time also takes into account heating time. X-ray powder diffractograms recorded at different temperatures are shown in Figure 8.

In the following examples which illustrate but in no way limit the present invention, the best modes of the preparation of novel pharmaceutically useful forms of losartan including new methods of purification and isolation of the present invention are presented.

Example 1
(Preparation of an amorphous potassium salt of losartan)

29.3 g of purified losartan was suspended in 293 ml of water. At room temperature pH was adjusted to 9.3 with a 10% aqueous potassium hydroxide solution. The reaction mixture clarified. The solution was filtered and lyophilized to yield 31.8 g of white, completely amorphous product losartan potassium.

Example 2
(Preparation of an amorphous potassium salt of losartan by evaporation)

1.0 g of a potassium salt of losartan of form I was dissolved in 20 ml of methanol or ethanol. The clear solution was filtered and evaporated *in vacuo* to the dry residue at 50 °C. Yield 1.12 g.

Example 3
(Preparation of an amorphous potassium salt of losartan by evaporation)

1 g of a potassium salt of losartan of form I was dissolved in 100 ml of *i*-propanol or 30 ml of *n*-propanol. The clear solution was filtered and evaporated *in vacuo* to the dry residue at 50°C. Yield 1.1 g.

Example 4
(Formation of polymorphic form III of losartan potassium from losartan potassium of form I in wet diethylether)

10.0 g of a potassium salt of losartan (form I) was suspended in 500 ml of diethylether. During vigorous stirring 5 ml of water was added to the suspension at room temperature, whereat water partially dissolved in ether. It was stirred overnight and the formed precipitate was filtered and dried *in vacuo* at 45°C for 2 hours. Yield 9.5 g.

Example 5
(Formation of form III of losartan potassium from losartan potassium of form I in wet ethyl acetate)

10.0 g of a potassium salt of losartan (form I) was suspended in 500 ml of ethyl acetate. During vigorous stirring 5 ml of water was added to the suspension at room temperature. It was stirred overnight and the formed precipitate was filtered and dried *in vacuo* at 45°C for 3 hours. Yield 9.3 g.

Example 6
(Formation of polymorphic form III with the traces of form I of potassium salt of losartan)

10 g a potassium salt of losartan (form I) was suspended in 500 ml of diisopropylether. During vigorous stirring 1.2 ml of water was added to the suspension at room temperature. It was stirred overnight and the formed precipitate was filtered and dried *in vacuo* at 45°C for 3 hours. Yield 9.6 g.

Example 7

(Conversion of losartan potassium of form I in wet heptane)

10 g of a potassium salt of losartan (form I) was suspended in 100 ml of n-heptane. During vigorous stirring 1.2 ml of water was added to the suspension at room temperature. It was stirred overnight and the formed precipitate was filtered and dried *in vacuo* at 45°C for 3 hours. Yield 10 g. Polymorphic form III was principally formed. The product might contain other polymorphic forms in traces.

Example 8

(Formation of form III of losartan potassium from losartan potassium of form I in water)

5.0 g of a potassium salt of losartan (form I) was dissolved in 2.5 ml of water in a 10-ml reaction flask at room temperature. After about 5 minutes the product crystallized. The flask with the contents was dried *in vacuo* at 50°C for 6 hours, the contents were transferred to the mortar, ground and dried again in *vacuo* for 3 hours. Yield 4.3 g of the product.

Example 9

Formation of form III of losartan potassium in water and by washing with diethyl ether)

1.0 g of a potassium salt of losartan was dissolved in 0.5 ml of water at room temperature. After about 5 minutes the product crystallized, 50 ml of diethylether (or DIPE) was added and vigorously stirred for 1 hour to suspend. The resulting precipitate was filtered and dried in *vacuo* at 45 °C 2 hours. Yield 1.0 g.

Example 10

(Formation of form III of losartan potassium from losartan potassium of form I in water and by washing with diisopropylether)

1.0 g of a potassium salt of losartan (form I) was dissolved in 0.5 ml of water at room temperature. After about 5 minutes the product crystallized, 50 ml of diisopropylether was added and vigorously stirred for 1 hour to suspend. The resulting precipitate was filtered and dried in *vacuo* at 45 °C 3 hours. Yield 1.0 g.

Example 11

(Formation of form III of losartan potassium from losartan potassium of form I in water and by washing with heptane)

1 g of a potassium salt of losartan (form I) was dissolved in 0.5 ml of water at room temperature. After about 15 minutes the product crystallized, and while stirring vigorously 10 ml of *n*-heptane was added and stirred overnight. The resulting precipitate was filtered and dried. Yield 1 g.

Example 12

(Formation of form III of losartan potassium from amorphous losartan potassium in wet heptane)

1 g of an amorphous potassium salt of losartan was suspended in 10 ml of n-heptane. While stirring vigorously 0.12 ml of water was added to the suspension at room temperature. It was stirred overnight, the formed precipitate was filtered and dried. Yield 0.85 g.

Example 13

(Formation of form III of losartan potassium from amorphous losartan potassium in wet diethylether)

1 g of an amorphous salt of losartan was dissolved in 0.5 ml of water at room temperature. After about 15 minutes the product crystallized, 50 ml of diethylether was added and stirred vigorously overnight. The resulting precipitate was filterer and dried. Yield 0.9 g.

Example 14

(Formation of form III of losartan potassium from amorphous losartan potassium in wet ethyl acetate)

1.0 g of an amorphous potassium salt of losartan was suspended in 10 ml of ethyl acetate. While stirring vigorously 0.12 ml of water was added to the suspension at room temperature. It was stirred overnight and the resulting precipitate was filtered and dried *in vacuo* at 45 °C 3 hours . Yield 0.87 g.

Example 15

(Formation of form III of losartan potassium from amorphous losartan potassium in water and by washing with diethylether)

1.0 g of an amorphous salt of losartan was dissolved in 0.5 ml of water at room temperature. After about 15 minutes the product crystallized, 50 ml of diethyl ether was added and stirred vigorously overnight. The resulting precipitate was filtered and dried in *vacuo* at 45 °C 3 hours. Yield 0.9 g.

Example 16

(Formation of form III of losartan potassium from amorphous losartan potassium in humid atmosphere)

Amophous losartan potassium (about 0.5 g) was uniformly distributed on the bottom of the Petri dish and uncovered placed in the desiccator with controlled relative humidity (80%, KBr solution). The sample dissolved after about 45–60 minutes (a transparent viscous mass was formed), and then crystallized (white crystals were produced).

Example 17

(Thermogravimetric analysis)

The content of water in form III of losartan potassium was determined by thermogravimetric analysis.

According to the calculation, trihydrate substance contained 10.5% of water, there was a 3.5% change in the weight because of one water. TG measurements clearly indicated that water loss occurred in two steps. The limit between the steps was between 50°C and 60 °C wherein in the first step the sample lost about 3 to 4% of the weight, in the second step about 7 to 8%, and totally about 12%. .

Example 18
(DVS measurements)

In the DVS experiment, in the starting amorphous sample the weight increased by 20–26% at 70–80% relative humidity. At higher increase of relative humidity, the weight of the sample decreased to below about 13% of water which indicated crystallization. From the amorphous state a crystal structure crystallized whereat surplus water separated from an orderly-state structure which could be visualized as a sudden drop of the weight. In the repetitive circle of sorption/descorption of water, the moisture in the sample did not increase above the equilibrium moisture in the crystal (absorbed less water than previously the amorphous form). DVS measurements also confirmed that it was the crystal-bound water, because they clearly showed that during drying of the crystal substance, there was no loss of moisture. It was lost relatively quickly at the end when the relative humidity dropped below 20%.
During heating under reduced pressure (at about 0.3 mbar) crystal-bound water was lost and the formed substance was amorphous again.

Example 19
(DSC analysis of amorphous potassium salt of losartan)

DSC diagram of amorphous losartan potassium salt was recorded. To 110°C a stretched endothermic peak was visible denoting loss of water. At 128–129°C there was a saddle denoting a glassy conversion of the amorphous substance. At 201–220°C there was a well-marked peak resulting from an orderly-state structure into the crystal lattice (crystallization). Later on DSC curve no conversion to the other polymorphic form was visible as it was visible during heating of crystalline

polymorphic form I which converted to Form II at 240°C. Crystals of the substance began to melt at 273°C, melting was followed by decomposition which was identical as in the crystalline substance.

Example 20
(DSC analysis of form III of potassium salt of losartan)

DSC diagram of polymorphic form III of potassium salt of losartan was recorded. To 75°C a stretched peak was visible denoting loss of first water, about 90°C a sharp endothermic peak denoting simultaneous loss of the other two waters and destruction of the ordered state to amorphous (an amorphous form of the substance has a higher level of disordered state and thus higher entropy than a crystal form, therefore the conversion of a crystal to an amorphous form is an endothermic process). At 190–200°C the amorphous substance crystallized again.

Example 21
(Stability)

Amorphous losartan potassium was essentially more hygroscopic than crystalline losartan potassium of form III. For evaluation and comparison, respectively, of the stability, four examples were conducted. The amorphous substance was compared with polymorphic form III, both exposed 4 days in the atmosphere of air under the conditions:

Example a: 60°C, dry atmosphere
Example b: 60°C, moisture
Example c: 80°C, dry atmosphere
Example d: 80°C, moisture

The results indicated that polymorphic form III was at least as stable as amorphous (to temperature and moisture). Exposed to moisture amorphous losartan potassium merged into a glassy mass and then white crystals of Form III were formed; in the parallel example, polymorphic form III of losartan potassium maintained a powdered form when exposed to moisture.

Both forms of substances were very similar by the assays of degradation products.

Example 22
(Dependence of XRD on temperature)

A sample of polymorphic form III of losartan potassium was recorded at temperatures: 25, 40, 60, 90, 120 and 240°C. Heating to individual temperature was at the rate of 10°C/min. Measurement at one temperature lasted 50 minutes. Total time of measurement was 7 hours and 22 minutes. That time also takes into account heating time. The amorphous substance was formed from polymorphic form III above about 60°C which crystallized at a temperature to about 240°C again.

Claims

1. Polymorphic form III of potassium salt of losartan characterized in that it exists in the crystal form with the bound water and its X-ray powder diffractogram exhibits diffractions at about 13.0, 17.2, 19.7, 20.9, 21.0, 23.2, 23.6, 24.5, 25.0, 26.6, 17.3, 28.2, 29.0, 31.5 degrees 2θ.

2. The polymorphic form III of potassium salt of losartan according to claim 1 characterized in that it exists in the crystal form with the bound water wherein the amount of water is between about 7 and 12 wt. %.

3. The polymorphic form III of the potassium salt of 2-n-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole characterized in that it crystallizes in a form of dihydrate.

4. The polymorphic form III of potassium salt of losartan according claim 2 characterized in that in the thermogravimetric analysis it loses about 4% of the weight when heated to about 55°C, and then loses about 8% of the weight when heated above about 55°C.

5. The process for the preparation of the polymorphic form III of potassium salt of losartan the characterized by conversion of a potassium salt of losartan in the presence of water.

6. The process according to claim 5 characterized in that water is present as moisture.

7. The process according to claim 6 characterized in that polymorphic form III of potassium salt of losartan is prepared from amorphous losartan potassium so that amorphous losartan potassium is exposed to the atmosphere with about 20% to about 80% relative humidity.

8. The process according to claim 5 characterized in that water is present in a mixture of solvents which are immiscible or poorly miscible with water.

9. The process according to claim 5 characterized in that it comprises the following steps:

a) preparation of a concentrated aqueous solution of a potassium salt of losartan in about 0.4- to about 1.2-fold amount of water to the weight of losartan,

b) Isolation of polymorphic form III from a mixture of solvents by drying and grinding.

10. The process according to claim 8 characterized in that it comprises the following steps:

a) preparation of a concentrated aqueous solution of a potassium sat of losartan in about 0.4- to about 1.2-fold amount of water to the weight of losartan,

b) addition of a solvent immiscible or poorly miscible with water to the resulting solution,

c) Isolation of polymorphic form III from the resulting mixture of solvents.

11. The process according to claim 8 characterized in that it comprises the following steps:

a) suspending of a potassium sat of losartan in a mixture of water-immiscible solvents and water in a molar ratio of about 3 to about 30 to losartan,

b) Isolation of polymorphic form III from the resulting mixture of solvents.

12. The process according to claims 10 or 11 characterized in that a solvent is selected from the following solvents: diethylether, diisopropyether, butylmethylether, pentane, hexane, heptane, cyclohexane, methylcyclohexane, benzene, toluene, xylene, ethyl acetate, propyl acetate, butyl acetate.

13. Polymorphic form III of losartan potassium salt characterized in that it is prepared by the process as defined in any of claims 5 to 12.

14. Amorphous form of losartan potassium prepared by evaporation of the alcoholic solution of losartan potassium.

15. The pharmaceutical composition containing as the active substance polymorphic form III of potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole.

16. The use of polymorphic form III of a potassium salt of losartan for the preparation of a medicament.

17. The use of polymorphic form III of a potassium salt of losartan according to claim 16 for the preparation of a medicament for the treatment of hypertension.

18. The process for the preparation of amorphous salt of losartan potassium characterized in that the bound water is removed from the polymorphic form III of potassium salt of losartan.

Lek Pharmaceuticals d.d.

Abstract

A new crystalline form of pharmaceuticaly suitable salt of 2-*n*-butil-4-kloro-5-hidroksimetil-1-[[2'-(1H-tetrazol-5-il)[1,1'-bifenil]-4-il]metil]-1H-imidazola with bound water has been prepared by rearrangement of other polymorph form into such.

New form can be prepared from amorphous structure in moist atmosphere or from concentrated aqueous suspension or solution thereof in mixture of solvents with water, that do not mix with water.

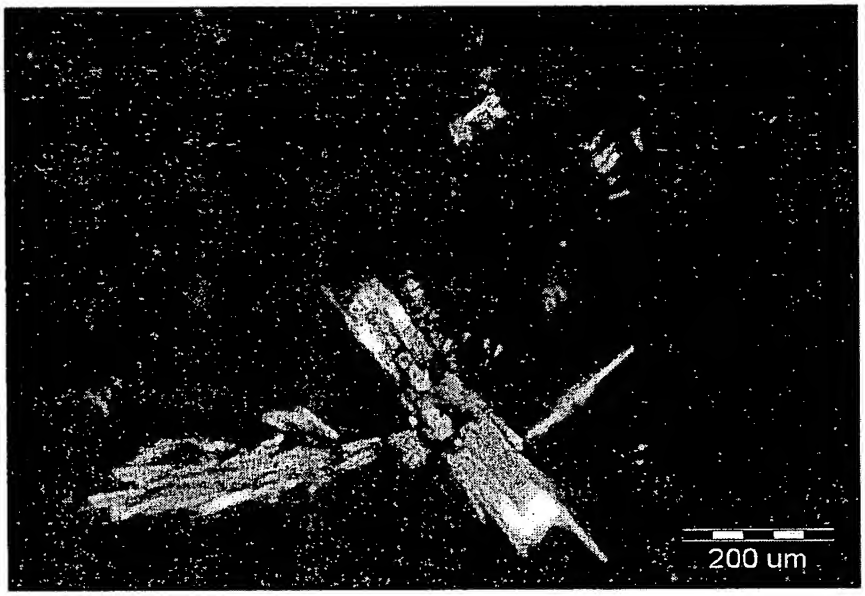

Figure 1

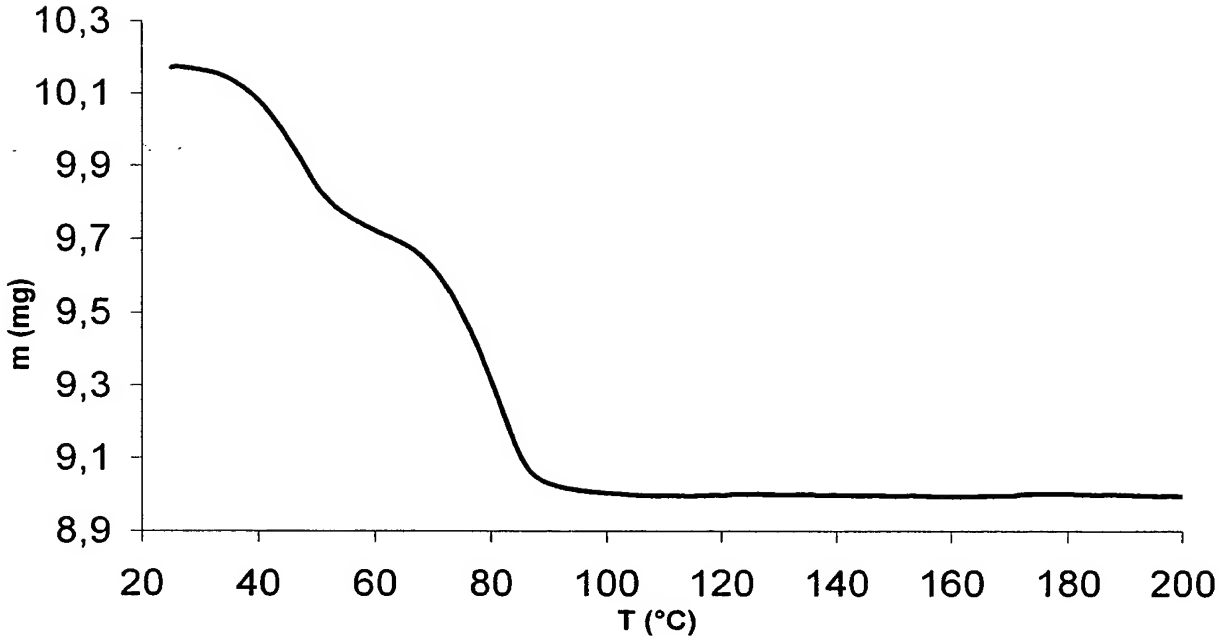

Figure 2

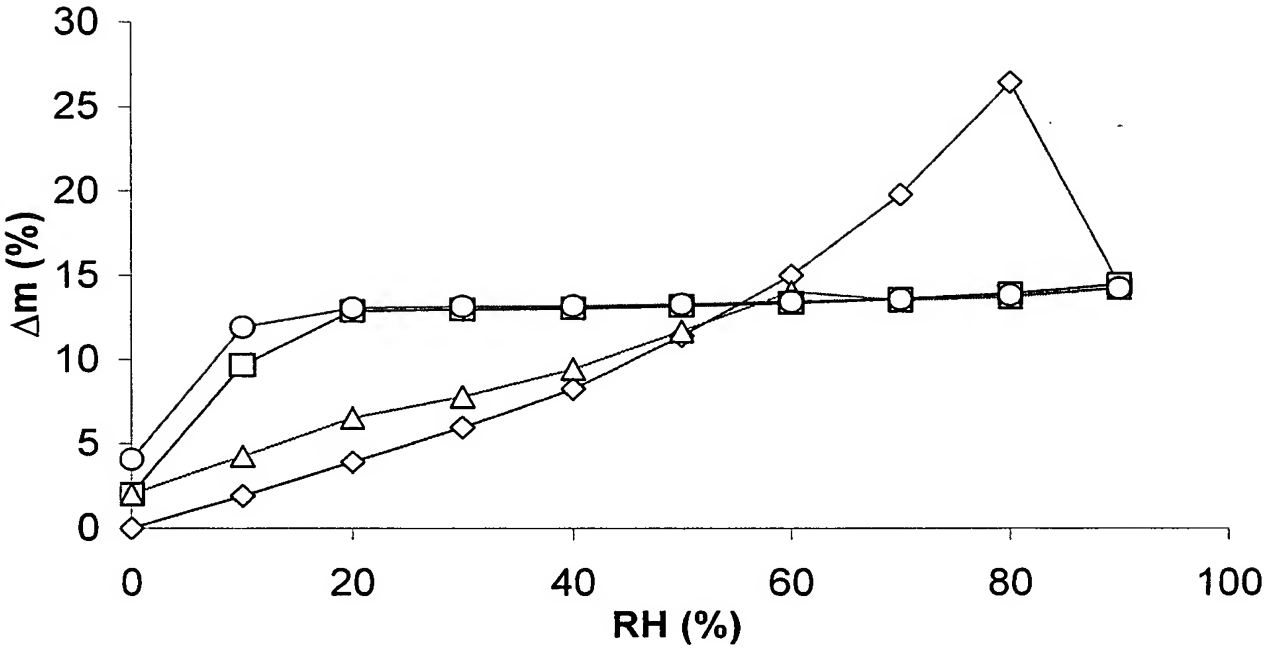

Figure 3

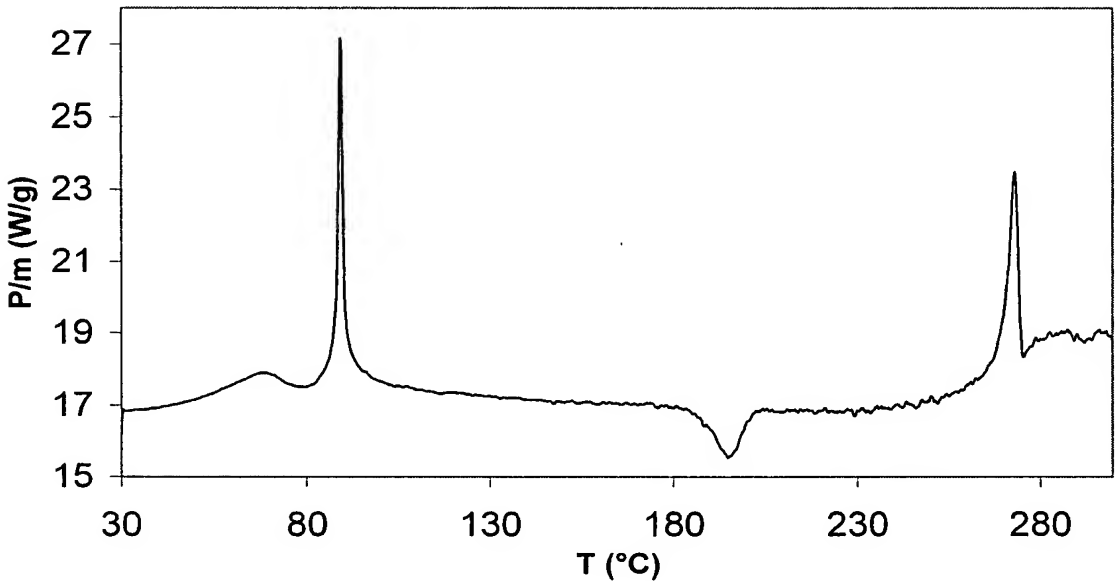

Figure 4

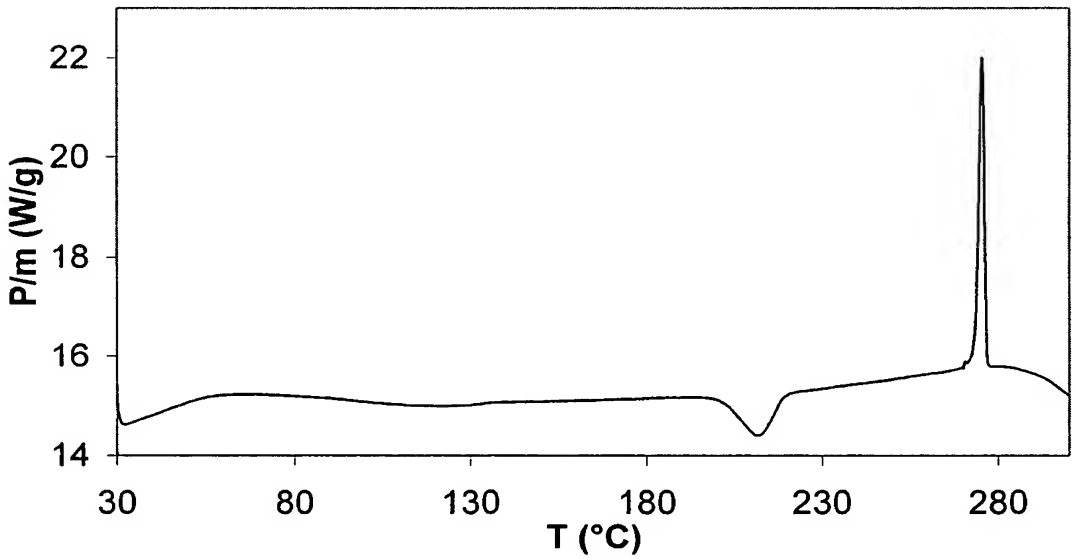

Figure 5

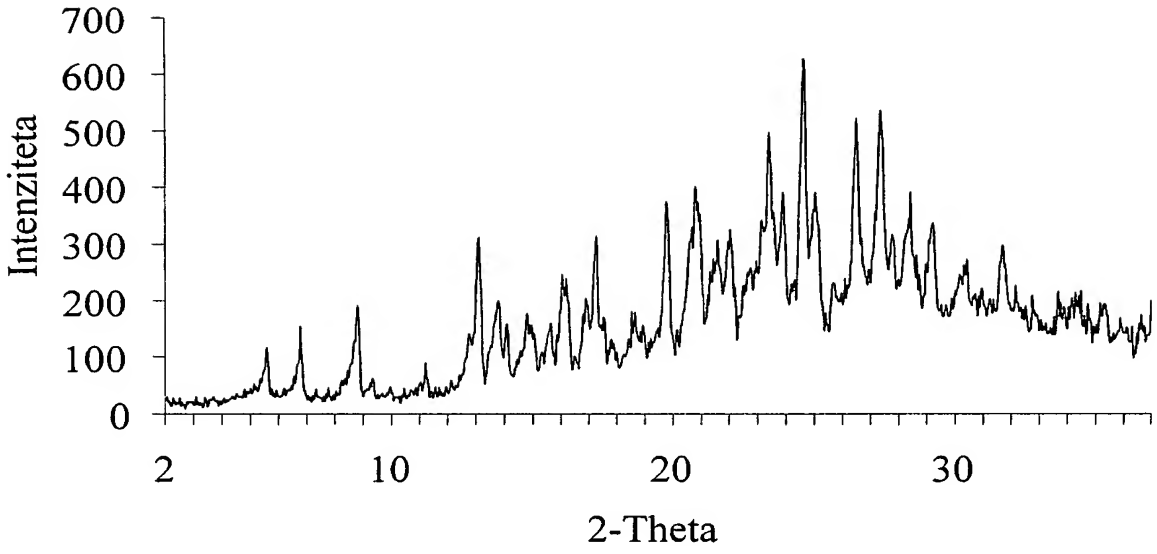

Figure 6

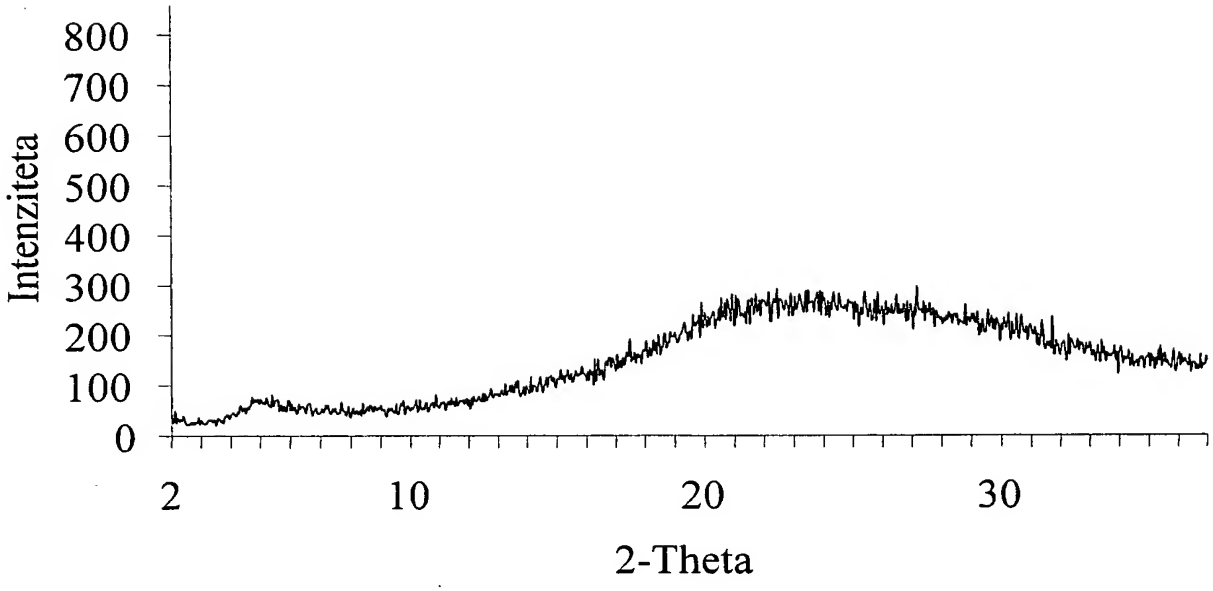

Figure 7

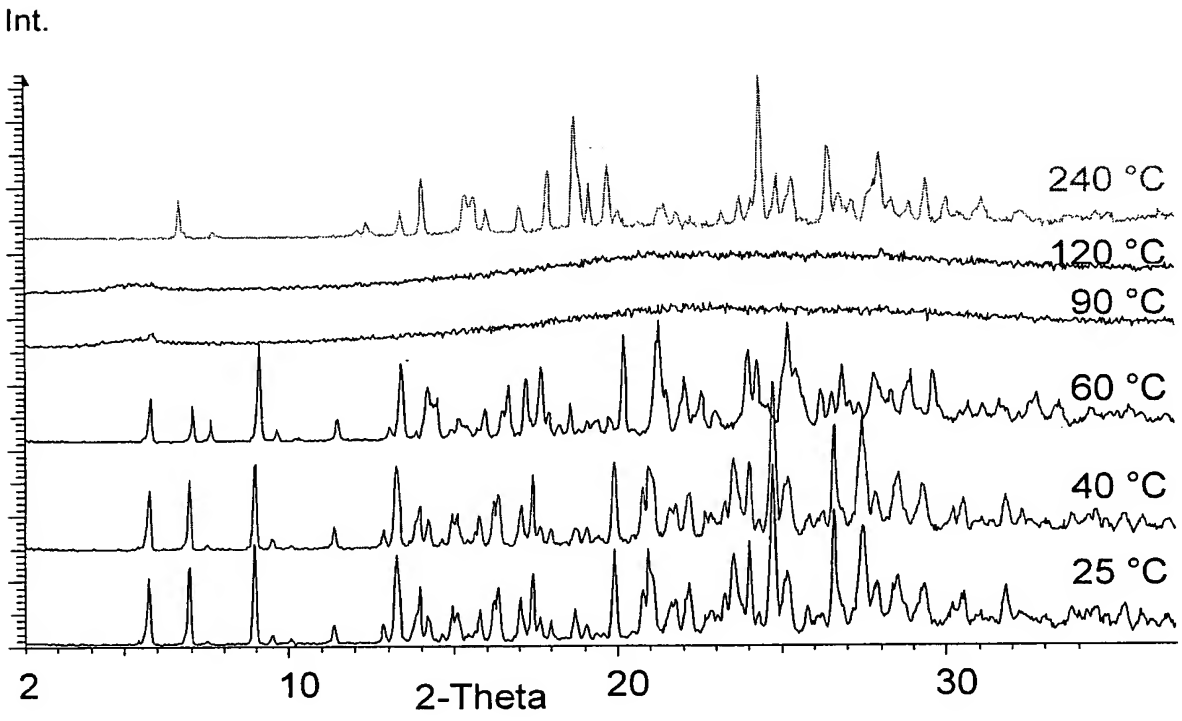

Figure 8

The undersigned Djurdjica Mandrino, permanent court interpreter for the English language, appointed by Decree No. 756-4/91, issued on 11th of February 1991 by the Ministry of Justice and Administration, Republic of Slovenia, hereby declares that this document entirely corresponds to the original Slovene text.

Ljubljana, 8 June 2005

STALNI SODNI TOLMAČ ZA ANGLEŠKI IN SRBOHRVAŠKI JEZIK
MANDRINO DJURDJICA
Ane Zlherlove 14/29
LJUBLJANA